Exhibit 1-062107

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Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure

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OBJECTIVES. This study was undertaken to determine if a standard dose of aspirin interacts relevantly with the circulatory effects of enalapril in severe heart failure. BACKGROUND. The frequent association of heart failure with coronary artery disease confers potential for combined treatment with an angiotensin-converting enzyme inhibitor and the prostaglandin synthesis inhibitor aspirin, the pharmacodynamic actions of which are, in part, mutually opposed. METHODS. In 18 patients, on 3 consecutive days, hemodynamic measurements were performed at baseline and 4 h after administration of a double placebo, enalapril (10 mg) plus placebo and enalapril plus aspirin (350 mg) according to a double-blind, randomized, crossover protocol. RESULTS. Enalapril given before aspirin led to significant decreases in systemic vascular resistance, left ventricular filling pressure and total pulmonary resistance together with a significant increase in cardiac output. When given with or on the day after aspirin, enalapril did not elicit significant changes in any of these variables. There was a clear tendency to lower values for pulmonary artery pressure on all regimens, and slowing of the heart rate was incurred whether or not aspirin had been given. Chi-square analysis of the individual responses showed that the probability of effecting a decrease in systemic vascular resistance > or = 300 dynes.s.cm-5 was six times greater when enalapril was given without aspirin ($p < 0.01$). CONCLUSIONS. In severe heart failure, the prostaglandin synthesis inhibition by aspirin counteracts the systemic arterial vasodilation of angiotensin-converting enzyme inhibition with enalapril and substantiates its dependence on the integrity of prostaglandin metabolism. Trends toward reductions of pulmonary artery pressure and slowing of the heart rate were still observed, presumably subsequent to lowered norepinephrine concentrations indicating maintenance of prostaglandin-independent actions of angiotensin-converting enzyme inhibition.

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